Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 1211–1221

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

9

The risk of obstetrical syndromes after solid organ transplantation

Ivo Brosens, MD, Professor [a, *], Jan J. Brosens, MD, Professor [b], Giuseppe Benagiano, MD, Professor [c]

[a] Leuven Institute of Fertility and Embryology, Leuven, Belgium
[b] Division of Reproductive Health, Warwick Medical School, Coventry CV2 2DX, United Kingdom
[c] Department of Gynecology, Obstetrics and Urology, Sapienza, University of Rome, Rome, Italy

Keywords:
solid organ transplantation
pregnancy outcome
complications

Pregnancy after solid organ transplantation is perfectly possible, but it is associated with an increased risk of major obstetrical complications including pre-eclampsia, foetal growth restriction and preterm birth.

Following liver and kidney grafting, the risk of complications is higher especially after kidney transplant, reflecting pre-existing hypertensive and vascular disease. In these patients, prevention should start before the onset of pregnancy through normalisation of hypertensive and vascular conditions.

Following heart and lung transplants, the risk of rejection during and after pregnancy remains significant and an adequate immunosuppression is imperative, especially after lung transplants because of their intrinsic high rate of rejection.

A likely explanation for the higher risk of pregnancy complication is an alteration of the 'placental bed', the decidua and the inner myometrium underlying the placenta, a zone encompassing the full length of the spiral arteries supplying maternal blood to the placenta. Unfortunately, this zone has not been investigated in pregnancy after solid organ transplantation.

* Corresponding author. Leuven Institute for Fertility and Embryology, Tiensevest 168, B-3000 Leuven, Belgium. Tel.: +32 16270190; Fax: +32 16270197.
E-mail address: ivo.brosens@med.kuleuven.be (I. Brosens).

http://dx.doi.org/10.1016/j.bpobgyn.2014.08.001
1521-6934/

Introduction

The first woman to receive a kidney from her identical twin sister conceived within 2 years of the transplantation and delivered twice, by caesarean section, two healthy babies after carrying both pregnancies to term [1]. However, it is noteworthy that since the donor was an identical twin, immune suppression was not an issue and pregnancy was facilitated. Pregnancy is integral to expectations of women following vital organ transplantation. Unfortunately, despite thousands of successful pregnancies in solid organ transplant recipients, information regarding the outcome of these pregnancies remains limited [2]. The available data to evaluate the risk of the major obstetrical syndromes after solid organ transplantation come from transplantation pregnancy registers, including the National Transplantation Pregnancy Registry (NTPR) [3], the United Kingdom Transplant Pregnancy Registry [4], the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and the Australian National Perinatal Epidemiology and Statistics Unit (NPESU) [5,6]. While today more data are available, studies on the pathophysiology of pregnancies in transplanted women are still lacking.

Major obstetrical syndromes include pre-eclampsia or pregnancy-induced hypertension, preterm birth and foetal growth restriction. In this contribution, we examine the incidence of major obstetrical syndromes following different solid organ transplantation, including kidney, liver, heart and lung. The critical uterine functions affected by solid organ transplantation and the risks associated with uterus transplantation are discussed. Improved understanding of the pathogenesis of the major obstetrical complications and early diagnosis will hopefully improve the outcome.

Major obstetrical syndromes in pregnant solid organ recipients

Successful pregnancy is possible after solid organ transplantation, but the risk of major obstetrical disorders, including pre-eclampsia, preterm birth and foetal growth restriction, is high.

Kidney and liver transplants

Systematic reviews and meta-analyses of articles have recently evaluated pregnancy outcomes in recipients of kidney and liver transplants. The Kidney Transfer Review reported on 4706 pregnancies in 3570 recipients [7]; the Liver Transfer Review included 450 pregnancies in 306 recipients [8]. The comparison of pregnancy outcomes after kidney and liver transplantation in the United States shows a significant increase in the risk of major obstetrical complications, including pre-eclampsia, preterm delivery and low birth weight (Table 1).

A recent population study, based on data from the ANZDATA and the NPESU, reported on 695 pregnancies in 447 kidney transplant recipients [9]. The mean gestational age at birth was 35 ± 5 weeks in transplant recipients, significantly shorter than the national average of 39 weeks ($P < 0.0001$). The mean live birth weight for transplant recipients was lower than the national average (2485 ± 783 vs. 3358 ± 2 g), a difference that remained significant after controlling for gestational age. The authors concluded that, although transplant pregnancies are generally successful, outcomes differ from the general population in terms of perinatal survival rate, indicating that these pregnancies remain high risk in spite of good allograft organ function.

Heart and lung transplantation

The first successful pregnancy after heart transplantation was reported in 1988 [10]. The Heart Transfer Review by Cowan et al. [11] included 103 pregnancies in 58 recipients whereas the Lung Transfer Review by Shaner et al. [12] analysed 30 pregnancies with 32 outcomes (one triplet) in 21 female lung transplant recipients. Ten of the 21 recipients received a transplant because of cystic fibrosis and accounted for 12 pregnancy outcomes (seven live births, three spontaneous and two therapeutic abortions).

The risk of pre-eclampsia increases after cardiac transplantation. In the NTPR, the incidence of pre-eclampsia for cardiac recipients was 18% (Table 2), lower than that seen in kidney transplant recipients, but higher than the 2–7% in healthy nulliparous women [13]. Wu et al. [14] reviewed the outcome of

Table 1
Risk of obstetrical syndromes after kidney and liver transplantation in the US.

	Kidney[a] ($n = 4706$)	Liver[b] ($n = 450$)	Frequency in US population
Pre-eclampsia	27%	21.9%	3%
Preterm birth (<37 weeks)	45.6%	39.4%	12.5%
Birth weight (mean)	2420 g	2866 g	($p < 0.001$)

[a] Deshpande et al., 2011 [6].
[b] Deshpande et al., 2012 [7].

pregnancies after thoracic organ transplantation and concluded that the risk of rejection during and after pregnancy remains significant, rendering it necessary to maintain an adequate immunosuppression. This is especially true for lung transplants, which have a high rate of rejection independently of pregnancy status. As emphasised by the authors, with a 5-year mortality rate of 50%, it is paramount to counsel lung transplant patients regarding the impact of pregnancy on survival and their ability to participate in raising the child.

Co-morbidities

A number of associated factors, such as age, parity, chronic hypertension or renal disease, determine the risk of pregnancy complications, including miscarriage and gestational diabetes, in the solid organ recipient even more than the type of transplant. Chronic hypertension is a strongly unfavourable factor in all four groups of transplantation (Table 3), and associated with early-onset pre-eclampsia, foetal growth retardation and foetal death [13]. The high frequency of chronic hypertension in kidney recipients may explain the excess of severe obstetrical disorders in this population. In a retrospective study, Wielgos et al. [15] compared maternal, neonatal and graft outcomes in pregnant women after kidney or liver transplantation. Complete data sets were collected in 38 pregnancies in 37 women. Pre-existing hypertension was present in 15 of 19 (79%) pregnant kidney recipients and in two of 19 (10.5%) pregnant women after liver transplantation ($P < 0.000$X). The incidence of pre-eclampsia was also more prevalent in pregnant kidney recipients (P 0.04). The mean gestational age at labour was lower in the kidney group (34.9 ± 3.56 vs. 37.5 ± 1.62, respectively; $P < 0.000$X). A similar relationship was observed with the incidence of preterm deliveries before 37 weeks of gestation (42% vs. 11%, respectively; $P < 0.02$) and small for gestational age (47% vs. 11%, respectively; $P = 0.008$). It can be concluded that pregnancies after solid organ transplantation, particularly those following kidney transplantation, carry a high risk of major obstetrical syndromes, which in many cases reflect the impact of the underlying hypertensive condition on the vascular remodelling associated with deep placentation [16].

Defective deep placentation in solid organ recipient pregnancies

Since its first description in 1958 by Dixon and Robertson [17], the placental bed has come to be recognised as a critical interface of pregnancy. The term 'placental bed' was coined to indicate that not the basal plate of the placenta but the underlying decidua and the inner myometrium (the so-called myometrial junction zone, or JZ) constitute the maternal part of the placenta (Fig. 1). This zone encompasses the full length of the spiral arteries supplying the maternal blood to the placenta. Instead of

Table 2
Risk of obstetrical syndromes after heart and lung transplantation, in the US.

	Heart[a] ($n = 103$)	Lung[b] ($n = 30$)
Pre-eclampsia	18%	3%
Preterm (<37 weeks)	38%	37%
Birth weight (mean)	2600 g	2206 g
Low birth weight (<2500 g)	39%	

[a] Cowan et al., 2012 (NTPR) [11].
[b] Shaner et al., 2012 (NTPR) [12].

Table 3
Co-morbid conditions before or during pregnancy.

	Kidney[a] ($n = 4706$)	Liver[b] ($n = 450$)	Lung[c] ($n = 30$)	Heart[d] ($n = 103$)
Age (mean)	29.0 years	28.6 years	NA	NA
Miscarriage	14.0%	15.6%	30.0%	32.0%
Hypertension	54.2%	27.2%	53.0%	39.0%
Gestational diabetes	8.0%	5.1%	23.0%	2.0%

NA: not available.
[a] Deshpande et al., 2011 [6].
[b] Deshpande et al., 2012 [7].
[c] Cowan et al., 2012 (NTPR) [11].
[d] Shaner et al., 2012 (NTPR) [12].

focusing on the lesions in the basal plate, which – like a battlefield – consists of intermingled placental and maternal cells, changes in the placental bed are the key to ensuring adequate maternal blood supply to the intervillous space of the placenta [18]. In pre-eclampsia, most spiral arteries, with the exception of few in the centre of the placental bed, fail to undergo physiological changes in their myometrial segments. In the case of pre-existing hypertension, these arteries develop, in a short space of time, severe hyperplastic changes with superimposed acute atherosis [19]. The analysis of placental bed biopsies and caesarean hysterectomy specimens confirmed that the inadequate development of the utero-placental vessels also causes foetal growth retardation [20]. Subsequent studies also reported an association between impaired spiral artery remodelling and placental abruption [21], preterm rupture of membranes [22] and preterm labour with intact membranes leading to preterm delivery [23]. Therefore, defective deep placentation is not a specific lesion, but different types of vascular changes underlie different major obstetrical disorders [16,24,25].

The placental vascular bed is more prone to developing obstructive atherosclerotic lesions in the presence of subclinical hypertensive disorders when compared to other vascular beds. For this reason, in kidney transplantation recipients, the increased risk of placental disease in the event of a pregnancy is present many years prior to transplantation. In these women, alterations in the endothelial cell morphology of glomerular capillaries, termed glomerular endotheliosis, also occur in unmodified spiral arteries and is characterised by endothelial cell swelling and lipid accumulation [26,27]. Fibrin deposition in the microvasculature is common. Affected women have an increased ratio of thromboxane A2 relative to prostacyclin (PGI2) in their urine and elevated plasma levels of endothelin [28,29]. Importantly, elevated factor VIII consumption and increased levels of cellular fibronectin precede the onset of clinical manifestations in pregnancy [30,31]. Deep haemochorial placentation in the human requires decidualisation of the endometrium and extends to the inner myometrial spiral arteries in association with the invasion of the interstitial and later intravascular cytotrophoblast. Impaired decidualisation of the myometrial spiral arteries predisposes for failed intravascular trophoblast invasion. Because the decidual process in the human is controlled by crosstalk between sex steroid hormones and locally released cytokines during the luteal phase of the cycle, the failure of subsequent deep placentation may already have been determined in the conception cycle [32].

Unfortunately, no systematic research of the endometrium and the placental bed has been performed to explain the high risk of obstetrical complications after solid organ transplantation.

Critical uterine functions

Decidualisation and embryo selection

Compared to most mammals, two unique but poorly understood features characterise reproduction in human: the high incidence of embryonic aneuploidies and 'spontaneous' decidualisation of the endometrium, meaning that this process is driven by endocrine cues independently from the presence or absence of an implanting blastocyst. A growing body of evidence indicates that the shift from embryonic to maternal control of the decidual process represents a pivotal evolutionary adaptation to the challenge posed by highly invasive and chromosomally diverse human embryos. This concept is

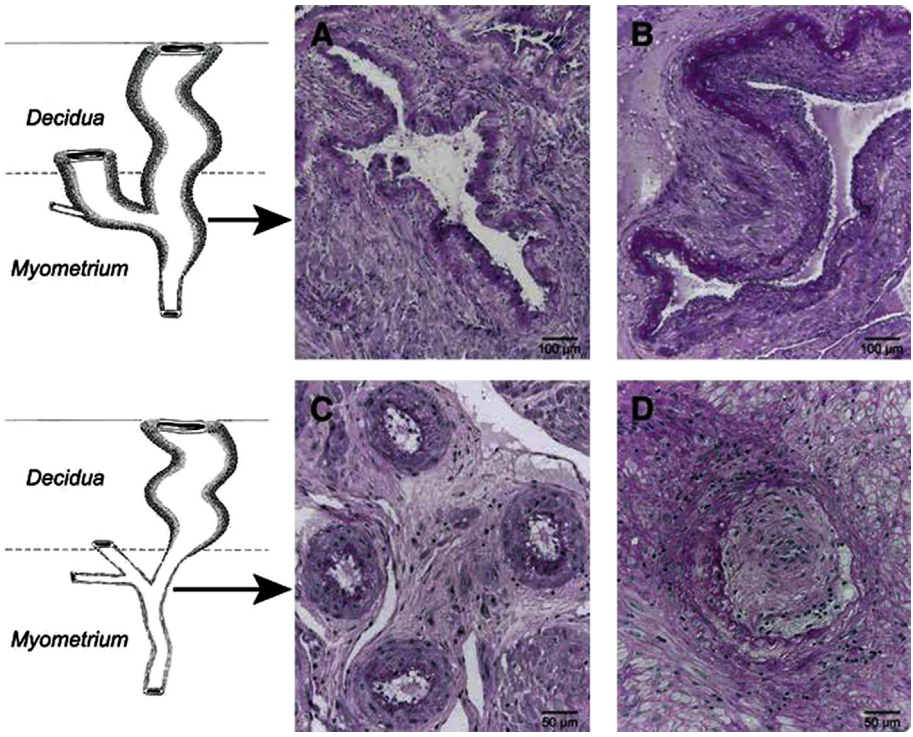

Fig. 1. Placental bed spiral arteries in normal pregnancy (A and B) and pregnancy with pre-eclampsia (C) and severe pre-eclampsia (D). A, Full transformation characterised by the loss of musculo-elastic structure and the presence of fibrinoid with cytotrophoblast; B, partial transformation; periodic acid–Schiff staining highlights the fibrinoid in A and B. C, Absent transformation (note trophoblastic giant cells surrounding the normal artery); D, obstructive lesions by acute atherosis and intimal hyperplasia and absence of transformation. *Reproduced, with permission, from Brosens* [16].

based on the ability of decidualised stromal cells to respond to individual embryos in a manner that either promotes implantation and further development or facilitates early rejection [33]. Furthermore, compelling evidence has emerged indicating that impaired decidualisation and lack of embryo selection are the major cause of early pregnancy loss and recurrent miscarriage [34–36]. Because of cyclic shedding and regeneration of the endometrium, the decidual process is intrinsically adaptable and capable of changing, perhaps accounting for the fact that most women suffering miscarriages will eventually be successful even without medical intervention [37].

At present, there have been no studies on the quality of the decidual response in non-pregnant recipients. These studies are needed as they may provide insight into the likelihood of miscarriage and the value of the luteal-phase progesterone support.

Vascular remodelling

Burton and Jauniaux [38] provided compelling evidence that early and late foetal development occurs in very different environments. During the first trimester, trophoblast plugging of the terminal spiral arteries ensures that there is little or no maternal blood flow to the early placenta. As a consequence, the oxygen tension within the foeto-placental unit is low and nutritive support for the conceptus is entirely dependent on secretions from the uterine glands and decidua. At the start of the second trimester, the maternal circulation within the intervillous space becomes fully established, oxygen tension rises and haemotrophic nutrition becomes dominant. During the transition part, there is a period of placental oxidative stress and the response of the tissues to the changing oxygen concentration

may play a pivotal role in determining the success or otherwise of the pregnancy. Plasencia et al. [39] demonstrated that maternal variables together with the uterine artery pulsatility index at between 11 and 13 completed weeks of gestation provide sensitive prediction of the development of pre-eclampsia, especially of the severe early-onset form. The net result of the intense tissue remodelling in the placental bed is the conversion of some 100 arteries into distended, funnel-shaped, tortuous vessels, the true utero-placental arteries. These vessels are devoid of musculo-elastic tissue and hence insensitive to vasomotor cues. The sole purpose of the transformation of these arteries is to accommodate the dramatic increase of maternal blood flow to the intervillous space as the pregnancy unfolds. Measurements in the third trimester showed that a perfusion rate of the uterus and placenta is approximately 750 and 600 ml per minute, respectively [40]. This perfusion rate represents approximately 25% of the cardiac output and a 17-fold increase from the rate of perfusion of a non-pregnant uterus [41].

Challenges to uterine functions in pregnancy after human uterus transplantation

In discussing uterus transplantation, it is of fundamental importance to realise that whereas the procedure is technically feasible [42] and pregnancy can be achieved [43], proof that in the human a transplanted uterus can sustain a normal pregnancy resulting in the birth of a healthy baby is still lacking.

In fact, this remains a highly contentious issue for a number of ethical and biological reasons. On the biological side, three main issues exist: First, the uterus is not a 'steady-state' organ like kidney, liver and most solid organs but requires great plasticity of the anastomosed vessels to accommodate the increase of bloodstream during the second half of pregnancy. With respect to uterus transplantation, the question arises how the extensive vascular adaptations associated with human deep placentation are tolerated after uterine artery anastomosis surgery, which inevitably is associated with scar formation particularly after a prolonged interval between surgery and pregnancy [44]. Second, while animal experiments have shown that a successful pregnancy can be achieved after uterus transplantation [45], these models are not representative for deep human placentation in which arterioles with a diameter of 50 μm must transform into large amorphic channels capable of accommodating 90% of the uterine blood supply to the intervillous space. Third, it is important to realise that the uterus cannot be viewed as an organ a priori designed to carry a pregnancy to term. For example, it is increasingly apparent that cyclic waves of spontaneous decidualisation, menstruation and endometrial regeneration play an important role in embryo selection at implantation and in the preconditioning of the vasculature prior to deep trophoblast invasion [46].

Is immunosuppression interfering with deep placentation?

Spiral artery remodelling and deep placentation involve the influx and presence of immune cells in the utero-placental interface. Immunosuppressive therapy may affect the role of the immune cells, such as the uterine natural killer cells and the T lymphocytes, in the decidua and the myometrial junction zone.

Data from the literature, as well as from reports from the NTPR, support the concept that immunosuppression be maintained at appropriate levels during pregnancy [47]. At present, most immunosuppressive maintenance regimens include combination therapy, usually cyclosporine or tacrolimus based. Most female transplant recipients will receive maintenance therapy prior to and during pregnancy. For some agents, including monoclonal antibodies and mycophenolate mofetil, there are either concerns or lack of safety data in pregnancy [47].

The question arises whether immunosuppression in pregnancy may interfere with the immunological process of deep placentation in the human. Romero et al. [25] emphasised the importance of understanding the physiology and pathology of transformation of the spiral arteries, and there are ample experimental data showing that changes in the immune cell population or function at the maternal–foetal interface contribute to the pathological pathways that cause obstetrical disorders. In a nested case–control study, Ogge et al. [48] (2011) investigated whether early-onset pre-eclampsia and late-onset pre-eclampsia have different pathophysiologies. They determined the prevalence of placental lesions attributable to persistent maternal under-perfusion in patients with pre-eclampsia as a function of gestational age. The study showed that the earlier the gestational age at delivery, the

higher the frequency of placental lesions consistent with maternal under-perfusion. Early- and late-onset pre-eclampsias seem to be a continuum with no clear and unambiguous gestational age at which lesions consistent with under-perfusion would be present. This state of under-perfusion with placental lesions has been linked to an imbalance in circulating concentrations of angiogenic versus anti-angiogenic factors [49].

Management of major obstetrical syndromes in solid organ recipients

Multidisciplinary approach

The collaboration of the obstetrician, paediatrician and transplant physicians before, during and after pregnancy and close monitoring of the recipient are mandatory for better pregnancy and graft outcome. The recommended time interval between transplantation surgery and conception should be at least 12 months and individualised according to the general health of the patient, maintenance presence of stable immunosuppressive levels, stable graft function and fertility potential of the patient [3].

Preconception counselling

A consensus conference organised by the Women's Health Committee of the American Society of Transplantation held in Bethesda, MD, in 2003 developed clinical guidelines for the transplant physician and obstetrical health providers [50]. Many uncertainties still exist, including the risks that pregnancy presents to the graft, the patient herself and the long-term risks to the foetus. The consequences of decreased gestational age at delivery, particularly <34 weeks of gestation, include neonatal death and long-term morbidities such as cerebral palsy, blindness, deafness and learning disabilities and low intelligence quotients. In addition, low birth weight is associated with increased hypertension, diabetes and coronary artery disease in adulthood [51]. These potential risks need to be discussed frankly with the prospective parents and hard ethical discussions entertained.

First-trimester diagnosis of major obstetrical disorders

There has been a great interest in the screening during the first trimester of women at risk of major adverse pregnancy outcomes, utilising both risk assessments and biomarkers. Several promising biomarkers have been proposed to identify women at the risk of subsequently developing pre-eclampsia, foetal growth restriction and spontaneous preterm birth [52].

Pre-eclampsia

Recent studies have suggested that low serum concentrations of human chorionic gonadotrophin (hCG) in very early pregnancy are associated with an increased risk of severe pre-eclampsia. Keikkala et al. [53] demonstrated in a nested case–control study that low concentrations of hyperglycosylated human chorionic gonadotrophin (hCG-h) in the first trimester are associated with subsequent pre-eclampsia especially in mothers with early-onset disease. The predictive value can be further improved by a combination of % hCG-h with pregnancy-associated plasma protein A (PAPP-A) and maternal risk factors. They concluded that the combination of hCG-h with PAPP-A and maternal risk factors identified such cases and that our findings are clinically relevant. It remains to be seen whether a combination of hCG-h with other markers and Doppler ultrasound measurements will further improve the diagnostic accuracy.

In a prospective cohort study, Åsvold et al. [54] linked pregnancies after in vitro fertilisation (IVF) to the Medical Birth Registry of Norway to obtain information on pre-eclampsia development. The study included 2405 consecutive singleton pregnancies and examined the association of maternal serum hCG concentrations on day 12 after embryo transfer with the risk of any pre-eclampsia and of mild and severe pre-eclampsia. HCG concentrations were inversely associated with pre-eclampsia risk in a dose-dependent manner (P trend 0.02). The inverse association was restricted to severe pre-eclampsia (P trend 0.01); thus, women with hCG <50 IU/l were at a fourfold higher risk of severe pre-eclampsia than

women with hCG ≥150 IU/l (absolute risk 3.6% vs. 0.9%; odds ratio (OR) 4.2, 95% confidence interval (CI) 1.4–12.2). For mild pre-eclampsia, there was no corresponding association (*P* trend 0.36). These results provide prospective evidence to support the hypothesis that impaired placental development may be associated with subsequent development of severe pre-eclampsia. Karahasanovic et al. [55] found in a smaller study that hCGβ was significantly lower in pregnancies that subsequently developed pre-eclampsia, although in this study no significant difference was found for PAPP-A.

The efficacy of measuring hCG, alone or in combination with soluble fms-like tyrosine kinase 1 (sFlt-1 or sVEGFR-1) and placental growth factor (PlGF), in predicting pre-eclampsia and preterm birth was further investigated in a nested case–control study [56]. This study found that high hCG concentrations (highest quartile) in the first trimester were associated with a reduced risk of preterm pre-eclampsia (OR 0.3, 95% CI 0.1–0.9), compared with low hCG (lowest quartile), whereas high hCG concentrations in the second trimester were associated with an increased risk of preterm pre-eclampsia (OR 4.0, 95% CI 1.8–8.9). High hCG concentrations in the third trimester were associated with an increased risk of term pre-eclampsia (OR 4.8, 95% CI 1.8–13.3). Concentrations of hCG above the median value combined with PlGF below the median in the second trimester were associated with a very high risk of preterm pre-eclampsia (OR 36.9, 95% CI 8.2–165.8). The results reflect an important role of hCG in the pathophysiological processes that lead to pre-eclampsia. The combined association of hCG and PlGF indicates a possible synergism between underlying biological pathways.

Foetal growth retardation

In a population-based prospective cohort study, Jaddoe et al. [57] showed that early foetal life might be a critical period for cardiovascular health in later life. In 1184 children with first-trimester foetal crown to rump length measurements, whose mothers had a reliable first day of their last menstrual period and a regular menstrual cycle, the body mass index, total and abdominal fat distribution, blood pressure and blood concentrations of cholesterol, triglycerides, insulin and C peptide at the median age of 6.0 (90% range 5.7–6.8) years were measured. The childhood body mass index fully explained the associations of first-trimester foetal crown to rump length with childhood total fat mass. They concluded that impaired first-trimester foetal growth is associated with an adverse cardiovascular risk profile in school-age children.

Therefore, early foetal life might be a critical period for cardiovascular health in later life. Savasan et al. [58] reviewed the second- and third-trimester serum and ultrasound markers predictive of ischaemic placental disease including limited first-trimester data. While current studies report a statistical association between marker levels and various adverse perinatal outcomes, the observed diagnostic accuracy is below the threshold required for clinical utility. An exception to this generalisation is uterine artery Doppler for the prediction of early-onset pre-eclampsia. Current guidelines published by the Society for Maternal Fetal Medicine in the United States recommend the following: (1) antepartum surveillance of a viable foetus with suspected intrauterine growth retardation includes umbilical artery Doppler; (2) in pregnancies complicated by intrauterine growth retardation, antenatal corticosteroids should be administered in the case of absent or reversed end-diastolic flow in the umbilical arteries <34 weeks; (3) pregnancies complicated by intrauterine growth retardation and absent end-diastolic velocities in the umbilical artery may be managed expectantly until delivery at 34 weeks as long as foetal surveillance remains reassuring; and (4) pregnancies complicated by intrauterine growth retardation and reverse end-diastolic velocities in the umbilical artery may be managed expectantly until delivery at 32 weeks as long as foetal surveillance remains reassuring [59].

Spontaneous preterm birth

While the risk assessment for spontaneous preterm birth using maternal characteristics or previous obstetric history alone is of poor predictive value [60,61], there are also no biochemical tests that have been shown to be strongly predictive of subsequent spontaneous preterm birth. A transvaginal ultrasound of cervical length is the mainstay of mid-trimester screening of high-risk women but recent data showed no correlation between first-trimester short cervix alone and subsequent preterm birth <34 weeks [62].

Summary

Pregnancy following solid organ transplantation is becoming relatively common, particularly after kidney and liver transplants. In all groups, however, major obstetrical syndromes are more frequent than in the general population. Obstetrical syndromes, including pre-eclampsia, preterm birth and foetal growth restriction, are higher for kidney than for liver or other solid organ transplantations. The causes of the obstetrical complications after solid organ transplantation may be complex although several important insights have emerged. First, solid organ transplantation increases the risk of defective deep placentation in a subsequent pregnancy. Kidney transplant recipients have the highest risk, presumably reflecting the presence of pre-existing hypertensive and vascular diseases. Second, the uterine vascular bed – in contrast to other vascular beds – needs to provide in the event of a pregnancy a unique vascular response with a great risk of developing obstructive, atherosclerotic lesions, even in the presence of subclinical hypertensive diseases. It has been shown that in women with renal disease a similar increased risk of complications already existed in pregnancies during the years before the transplantation. Third, immunosuppression may perturb vascular remodelling in pregnancy by affecting the key immune cells, such as uterine natural killer cells, present at the foeto-maternal interface. Unfortunately, no attempts have been made to obtain placental bed biopsies and study the vascular changes after organ transplantation. Meanwhile, the first attempts to transplant the uterus in order to obtain a pregnancy are performed. At present, the main advance for improving the outcome of a pregnancy after solid organ transplantation is the early detection of any underlying maternal hypertensive or vascular disorder. Meanwhile, the main target for improving the outcome of pregnancy in women at risk is the strict antihypertensive treatment from the earliest stage of pregnancy. Multidisciplinary care from the earliest stage of the pregnancy is required as signs of foetal growth restriction can be detected from the early stage of pregnancy.

Practice points

- Pregnancy after solid organ transplantation is associated with an increased risk of major obstetrical complications including preeclampsia, fetal growth restriction and preterm birth.
- The higher risk after kidney transplantation reflects a pre-existing presence of hypertensive and vascular disease.
- Prevention of major obstetrical syndromes should start before the onset of pregnancy by normalizing the hypertensive and vascular condition.

Research agenda

- Biomarkers for the detection of defective placentation in early pregnancy
- Morphological and molecular study of the placental bed in solid-organ recipients
- Optimal management of hypertension and cardiovascular disease in pregnant solid organ recipients
- Specific exploration of immunological issues relating to uterus transplantation

Disclosure

I.B. has nothing to disclose. J.J. has nothing to disclose. G.B. has nothing to disclose.

Conflict of interest

The authors report no conflict of interest.

References

[1] Murray JE, Reid DE, Harrison JH, et al. Successful pregnancies after human renal transplantation. New Engl J Med 1963; 269:341–3.
*[2] McKay DB, Josephson MA. Pregnancy after kidney transplantation. Clin J Am Soc Nephrol 2008;3(Suppl. 2):S117–25.
*[3] Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transplant 2010:65–85.
[4] Sibanda N, Briggs JD, Davison JM, et al. Pregnancy after organ transplantation: a report from the U. K. Transplant Pregnancy Registry. Transplantation 2007;83:1301–7.
[5] Shahir AK, Briggs N, Katsoulis J, et al. An observational outcomes study from 1966-2008, examining pregnancy and neonatal outcomes from dialysed women using data from the ANZDATA Registry. Nephrology (Carlton, Vic) 2013;18: 276–84.
[6] McDonald SP, Russ GR. Australian registries-ANZDATA and ANZOD. Transpl Rev (Orlando, Fla) 2013;27:46–9.
[7] Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. Am J Transplant 2011;11:2388–404.
*[8] Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver Transpl 2012;18:621–9.
[9] Wyld ML, Clayton PA, Jesudason S, et al. Pregnancy outcomes for kidney transplant recipients. Am J Transplant 2013;13: 3173–82.
[10] Lowenstein BR, Vain NW, Perrone SV, et al. Successful pregnancy and vaginal delivery after heart transplantation. Am J Obstet Gynecol 1988;158:589–90.
[11] Cowan SW, Davison JM, Doria C, et al. Pregnancy after cardiac transplantation. Cardiol Clin 2012;30:441–52.
[12] Shaner J, Coscia LA, Constantinescu S, et al. Pregnancy after lung transplant. Prog Transplant 2012;22:134–40.
[13] Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol 2013;209:544.e1–544.e12.
[14] Wu DW, Wilt J, Restaino S. Pregnancy after thoracic organ transplantation. Sem Perinatol 2007;31:354–62.
[15] Wielgos M, Szpotanska-Sikorska M, Mazanowska N, et al. Pregnancy risk in female kidney and liver recipients: a retrospective comparative study. J Matern Fetal Neonatal Med 2012;25:1090–5.
*[16] Brosens I, Pijnenborg R, Vercruysse L, et al. The "great obstetrical syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193–201.
[17] Dixon HG, Robertson WB. A study of the vessels of the placental bed in normotensive and hypertensive women. J Obstet Gynaecol Brit Emp 1958;65:803–9.
[18] Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 1967;93:569–79.
[19] Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1972;1:177–91.
[20] Brosens I, Dixon HG, Robertson WB. Fetal growth retardation and the arteries of the placental bed. Brit J Obstet Gynaecol 1977;84:656–64.
[21] Dommisse J, Tiltman AJ. Placental bed biopsies in placental abruption. Brit J Obstet Gynaecol 1992;99:651–4.
*[22] Kim YM, Chaiworapongsa T, Gomez R, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. Am J Obstet Gynecol 2012;187:1137–42.
[23] Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. Am J Obstet Gynecol 2003;189:1063–9.
*[24] Khong Y, Brosens I. Defective deep placentation. Best Pract Res Clin Obstet Gynaecol 2011;25:301–11.
[25] Romero R, Kusanovic JP, Chaiworapongsa T, et al. Placental bed disorders in preterm labor, preterm PROM, spontaneous abortion and abruptio placentae. Best Pract Res Clin Obstet Gynaecol 2011;25:313–27.
[26] Khong TY, Sawyer IH, Heryet AR. An immunohistologic study of endothelialization of uteroplacental vessels in human pregnancy – evidence that endothelium is focally disrupted by trophoblast in preeclampsia. Am J Obstet Gynecol 1992; 167:751–6.
[27] Ferris TF. Preeclampsia and postpartum renal failure: examples of pregnancy-induced microangiopathy. Am J Med 1995; 99:343–7.
[28] Fitzgerald DJ, Entman SS, Mulloy K, et al. Decreased prostacyclin biosynthesis preceding the clinical manifestation of pregnancy-induced hypertension. Circulation 1987;75:956–63.
[29] Taylor RN, Varma M, Teng NNH, et al. Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. J Clin Endocrinol Metab 1990;71:1675–7.
[30] Lockwood CJ, Peters JH. Increased plasma levels of ED1^{+} cellular fibronectin precede the clinical signs of preeclampsia. Am J Obstet Gynecol 1990;162:358–62.
[31] Redman CWG, Denson KWE, Beilin LJ, et al. Factor-VIII consumption in pre-eclampsia. Lancet 1977;2(8051):1249–52.
*[32] Brosens JJ, Pijnenborg R, Brosens IA. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies. Am J Obstet Gynecol 2002;187:1416–23.
[33] Brosens JJ, Salker MS, Teklenburg G, et al. Uterine selection of human embryos at implantation. Sci Rep 2014 Feb;6(4): 3894.
[34] Salker M, Teklenburg G, Molokhia M, et al. Natural selection of human embryos: impaired decidualization of endometrium disables embryo-maternal interactions and causes recurrent pregnancy loss. PLoS ONE 2010;5(4):e10287.
[35] Salker MS, Christian M, Steel JH, et al. Deregulation of the serum-and glucocorticoid-inducible kinase SGK1 in the endometrium causes reproductive failure. Nat Med 2011;17:1509–13.
[36] Salker MS, Nautiyal J, Steel JH, et al. Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss. PLoS ONE 2012;7(12):e52252.
*[37] Lucas ES, Salker MS, Brosens JJ. Reprint of: uterine plasticity and reproductive fitness. Reprod BioMed Online 2013;27: 664–72.

[38] Burton GJ, Jaunaiux E. Maternal vascularisation of the human placenta: does the embryo develop in a hypoxic environment? Gynecol Obstet Fertil 2003;29:503–8.
[39] Plasencia W, Maiz N, Bonino S, et al. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2007;30:742–9.
[40] Browne JC, Veall N. The maternal placental blood flow in normotensive and hypertensive women. J Obstet Gynaecol Br Emp 1953;60:141–7.
[41] Assali NS, Nuwayhid B, Zugaib M. Control of the uteroplacental circulation in health and disease. Eur J Obstet Gynecol Reprod Biol 1978;8:43–55.
[42] Ozkan O, Akar ME, Erdogan O, et al. Uterus transplantation from a deceased donor. Fertil Steril 2013;100:e41.
[43] Erman Akar M, Ozkan O, Aydinuraz B, et al. Clinical pregnancy following uterus transplantation. Fertil Steril 2013;100:1358–63.
[44] Benagiano G, Landeweerd L, Brosens I. Medical and ethical considerations in uterus transplantation. Int J Gynecol Obstet 2013;123:173–7.
[45] Ramirez ER, Ramirez-Nessetti DK, Nessetti MBR, et al. Pregnancy and outcome of uterine allotransplantation and assisted reproduction in sheep. J Min Invasive Gynecol 2011;18:238–324.
[46] Brosens JJ, Parker MG, McIndoe A, et al. A role for menstruation in preconditioning the uterus for successful pregnancy. Am J Obstet Gynecol 2009;200:615.e1–6.
[47] Armenti VT, Daller JA, Constantinescu S, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transplants 2006:57–70.
*[48] Ogge G, Chaiworapongsa T, Romero R, et al. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. J Perinat Med 2011;39:641–52.
[49] Soto E, Romero R, Kusanovic JP, et al. Late-onset preeclampsia is associated with an imbalance of angiogenic and antiangiogenic factors in patients with and without placental lesions consistent with maternal underperfusion. J Matern Fetal Neonatal Med 2012;25:498–507.
[50] McKay DB, Josephson MA. Reproduction and transplantation: report on the AST consensus conference on reproductive issues and transplantation. Am J Transplant 2005;5:1592–9.
*[51] Robinson R. The fetal origins of adult disease: no longer just a hypothesis and may be critically important in south Asia. Brit Med J 2001;322(7283):375–6.
[52] Sharp AN, Alfirevic Z. First trimester screening can predict adverse pregnancy outcomes. Prenat Diagn 2014;34:660–7.
[53] Keikkala E, Vuorela P, Laivuori H, et al. First trimester hyperglycosylated human chorionic gonadotrophin in serum – a marker of early-onset preeclampsia. Placenta 2013;34:1059–65.
[54] Åsvold BO, Eskild A, Vatten LJ. Human chorionic gonadotropin, angiogenic factors, and preeclampsia risk: a nested case-control study. Acta Obstet Gynecol Scand 2014;93:454–62.
[55] Karahasanovic A, Sørensen S, Nilas L. First trimester pregnancy-associated plasma protein a and human chorionic gonadotropin-beta in early and late pre-eclampsia. Clin Chem Lab Med 2014;52:521–5.
[56] Åsvold BO, Vatten LJ, Tanbo TG, et al. Concentrations of human chorionic gonadotrophin in very early pregnancy and subsequent pre-eclampsia: a cohort study. Hum Reprod 2014;29:1153–60.
[57] Jaddoe VWV, De Jonge LL, Hofman A, et al. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. Brit Med J (Online) 2014;348:g14.
[58] Savasan ZA, Goncalves LF, Bahado-Singh RO. Second- and third-trimester biochemical and ultrasound markers predictive of ischemic placental disease. Semin Perinatol 2014;38:167–76.
[59] Berkley E, Chauhan SP, Abuhamad A. Doppler assessment of the fetus with intrauterine growth restriction. Am J Obstet Gynecol 2012;206:300–8.
[60] Sananes N, Meyer N, Gaudineau A, et al. Prediction of spontaneous preterm delivery in the first trimester of pregnancy. Eur J Obstet Gynecol Reprod Biol 2013;171:18–22.
[61] Beta J, Akolekar R, Ventura W. Prediction of spontaneous preterm delivery form maternal factors, obstetric history and placental perfusion and function at 11–13 weeks. Prenat Diagn 2011;31:75–83.
[62] Parra-Cordero M, Sepulveda-Martinez A, Rencoret G, et al. Is there a role for cervical assessment and uterine artery Doppler in the first trimester of pregnancy as a screening test for spontaneous preterm delivery? Ultrasound Obstet Gynecol 2014;43:291–6.